

SPL ER/DL Subteam Meeting

Minutes -- July 21, 2010

DRLS discussion with Paul Loebach

During today's discussion, Paul Loebach, DRLS Team Leader, emphasized that the DRLS team was available to help with issues related to drug listing and importing. DRLS contact information is:

email: edrls@fda.hhs.gov

Telephone: 301-210-2840

DRLS prefers communication by email. Telephone coverage is staffed during normal business hours.

The following specific topics were discussed at the meeting:

1. API drug listing: Pharma is now routinely filing electronic registration and drug listings according to the procedures outlined in "FDA Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Drug Establishment Registration and Drug Listing" and are following the training that is being provided by FDA.

Based on our understanding, drug listing of API may be accomplished through inclusion of the API manufacturing site in the finished product drug listing file – when the API is manufactured by an establishment that is owned by the same parent/corporate entity. Some pharma are still having trouble importing API, when the API is not drug listed separately. I.e. the API is being held up at the port of entry. Import inspectors are asking pharma to provide information that we don't believe is required based on our understanding of this guidance. Eg API drug listing number. We find this surprising since this information is available via the eList system. In addition, the port inspectors seem to be unable to access and retrieve this current electronic data.

- a. Do port inspectors have access to the information in eList? If not, when do you foresee them having access?
- b. What is the best way to handle import issues? Long-term solution?

Meeting Discussion:

Historically, when the eList system was implemented, it started from scratch. The data from the old system was not migrated into the system. The initial instruction to FDA/import staff were to look in the old system first, then eList.

FDA is now instructing import agents to look in eList to find them...rather than the old DRLS system. Import agents do have access to the new system. There are some new agents, and training occurred as recently as last week. If companies do have problems or delays importing, these can be directed to the DRLS office.

Additionally, to facilitate importation and for compliance reasons, CDER still recommends that pharma list the API separately with its own NDC number -- rather than only including the API manufacturer in the finished product SPL drug listing. But, the drug listing and import process should work even if you don't list separately.

If sponsors do have problems, contact DRLS, and they will help you handle the situation .
Best way to contact: EDRLS@fda.hhs.gov. Leyla Rahjou-Esfandiary is the key triage person.

Additional note from Paul: There are currently internal FDA discussions about whether this process (ie including API manufacturer only in the drug listing of the finished product) meets drug listing needs.

Additional note from ER/DR Team: There is a lot of confusion within companies because different groups within our corporations handle import issues. SPL Coordinators should communicate broadly within their company. In addition, sponsors would appreciate as much advance notice from FDA about pending process changes.

2. “Old DRLS system”: Our (sponsors) understanding has been that the registration and listing data is being supplied by sponsors via eList. We still get questions, however, that suggest that DRLS staff are looking at the old system, with outdated information.
 - a. Is the ‘old system’ that held the data manually keyed in from paper forms still active?
 - b. If so, what are the reason(s) for keeping two systems with equivalent data?
 - c. And do you expect that the ‘old system’ will be closed down (‘decommissioned’)? If so, when?

Meeting Discussion:

Old drug listing data was not migrated to the eList system. Sponsors are not required to drug list in electronic format until there is a change to the labeling. Staff are now being instructed to look in the eList system first, before reverting back to the ‘old’ system.

The old system will be maintained until DRLS is satisfied that there is enough information in eList.

3. Labeler codes are being requested for new establishments: When we register a new establishment (and thus need to obtain a new FEI number), we are being asked to submit a new Labeler Code Request. This should not be required for establishments that are involved only in various manufacturing processes and are not involved in commercialized product.
 - a. Why do we get asked for a new Labeler Code Request submission when we ask for an FEI?

Meeting Discussion:

This shouldn’t be happening. If an establishment doesn’t need an NDC number, then there is no reason to have a labeler code. Sponsors should contact DRSL with information about the situation, and they will help resolve it.

The probable cause for the question is that firms are not providing enough information to allow identification in the DFARS system and then link to the DUNS system. If an establishment is asked for a labeler code, then firms should respond with both the DUNS and FEI numbers.

4. Establishment information by product/part: Many of our labels include multiple products / formulations....and /or parts of kits.... that are manufactured at different manufacturing sites.

There is no way to provide this information in the SPL that is submitted to eList, and pharma are getting questions from DRLS staff to supply this information.

- a. What is the best way provide details to DRLS staff related to questions when the SPL includes multiple establishments – eg different manufacturers for individual parts of the kit or different product formulations/pack sizes.
- b. Are changes planned for SPL data standards to allow this information to be captured within the SPL?

Meeting Discussion:

If sponsors receive questions via phone, they should provide the information requested – via phone, email, etc.

SPL does support having establishment information at the individual product level. However, current process/training is that establishment information be provided only at the higher (aka label) level. FDA is working on a change to the drug listing regulations in 21CFR Part207. If FDA decides to change the way that establishments are reported, then the instructions for creating SPL will have to change.

5. NDC code for component parts: Products may be packaged with multiple inner packaging components – eg a carton of 28 capsules may contain 4 blister cards of 7 capsules each; a parenteral product may contain a vial of active ingredient and a vial of diluent. We are being asked by DRLS staff to provide NDC codes (and thus drug list) for both the inner and outer packaging components and individual parts in a package/kit.

Our trend is to put an NDC code on most things as a way to identify it. However, we have concerns about providing NDC codes and drug listing non-saleable units.

- a. Please explain the rationale for this.
- b. Note: We acknowledge that it is logic for the CMS group to want to have an NDC code on an inner package -- if the package can be broken apart and parts dispensed separately. An example is a carton (outer package) containing 100 individually wrapped blister packages. These would be dispensed-and billed-within a hospital setting. The outer package would have an NDC indicating a pack of 100.....then each of the inner blisters would have an NDC code indicating a package of 1. This would allow the hospital to bill one capsule by an NDC code.

Meeting Discussion:

DRLS requires an NDC code for the complete product/kit. DRLS does not require NDC numbers to be on the individual components / parts of the kit.

However, DRLS systems can accommodate NDC numbers for inner components/parts. Sponsors should contact CMS for information / insight into what information they need and how the information is used.

6. Business Operation Terms:
 - a. Definitions of all active business operations (those with codes):
 - i. Can DRLS provide definitions of all business operation terms? This would improve consistent between terms used in the establishment registration and the drug listing.

- ii. For instance, Sterilize is a little too general. Would this include generation of water for injection since it is sterile? Is the intent to identify finished product sterilizers, e.g., Ethicon, Isomedix, etc.?
 - iii. Is Particle Size Reduction really needed? Particle size reduction happens in a lot of manufacturing operations both API and DP. Why is this included? One sponsor mentioned “it’s like including drying and mixing operations as separate categories.”
- b. Will DRLS be adding a category for Bulk Product (or Intermediate, or other)
- c. For the primary manufacturers that do multiple operations within any one establishment and/or within their parent company, we have been told by DRLS that the term “manufacture” includes the operations of “pack” and “label” and that there is no need to list these terms separately in either the DER or DL submissions. Are there any other terms that are included in the over-arching business operations terms of API manufacture and manufacture?
 - i. For manufacture, does this include any other business operations (eg sterilize, particle size reduction, analytical)?
 - ii. For API manufacture, does this include any other terms (eg, particle size reduction, analytical)?
- d. Which terms are specific for third party manufacturers? A table has been drafted with descriptions of business operation terms. The terms pack, label, and sterilize are already denoted as specific for use by third party contractors, but not for the primary manufacturer. Are there other terms, such as particle size reduction, that should be treated likewise?

Meeting Discussion:

DRLS agrees that there should be definitions for business operation terms. They have requested these definitions from the data standards council. These may be published in the future.

Several business operation terms have been created with the intent that they would be used by third party manufacturers. The goal is transparency for the manufacturing process.

FDA is continuing to have internal debate, as to whether new marketing category terms should be created for ‘bulk product’ and/or ‘intermediate bulk’. Currently, as long as the manufacturing site is included in the SPL, this will be acceptable for imports.

Note: the term API refers to Active Pharmaceutical Ingredient --ie 100% pure-- and not mixed in with other inactive ingredients.

7. Business Operation terms in DERs: Now that the validation rule for business operations matching between Establishment Registration and Drug Listing is important to know the terms that are registered for contract manufacturers. Sponsors do not have this information transparent and available for third party suppliers (CMOs).

A bit more information: Companies know what business operations have been registered in their own Establishment Registrations, but are not necessarily aware of what “third party suppliers” may have used for their business operations. For example, Third-Party ABC may have put “label” when they are actually “relabel”. A sponsor including Third-Party ABC’s DUNS number in a Drug Listing with the Business Operation of “relabel” would have their SPL bounce back as an error.

- a. Can you discuss the possibility of making available a list of business operations associated with each DUNS number in the eList/eDRLS system?

Meeting Discussion:

DRLS does not plan to publish this information. Sponsors can get this information by submitting an FOI request.

Sponsors have 2 options to resolve these validation errors:

1. Contact the contract manufacturer/establishment and ask them to provide their terms.
2. Lonnie has offered to help. Sponsors can contact him with individual requests for the business operation terms for a specific establishment. Lonnie is also interfacing with the API manufacturers who have improperly registered – in order to encourage them to correct their terms.

Question: Many of our SPL files are failing. Establishments have until the end of the year to register for 2010. Can we delay the validation rule until the end of the year?

DRLS response: During the meeting, the DRLS staff offered to follow-up about this possibility. The decision was made that these validation rules will remain in effect.

8. Drug Listing information and the CMS system: How does Dailymed tie into the CMS system?

Meeting Discussion:

DRLS publishes the NDC directory, and it is used by CMS for reimbursements. For additional facts and insight into how the information is used, contact CMS.

9. Update for the NDC Directory: When is the NDC Directory updated during the month?

Meeting Discussion:

The NDC directory is updated twice monthly, on or about the 1st and 15th of the month...and/or 1st business day afterward.

10. Managing questions from DRLS staff: Is it possible for industry to get a personal phone number from the DRLS staffer when FDA is the one to contact industry. I will receive a call, investigate and want to call back the person who called me, however, they will only provide the general call-in number. Then, we have to leave a message and wait for the person to phone back. Often times, this leads to many voice mail messages and lots of wasted time. It would be much more efficient to get the person's direct phone number. I would think this would save time for FDA, too.

Meeting Discussion:

DRLS prefers using email and/or the central number (301-210-2840). This number is staffed during normal business hours on the east coast.

11. Delisting 'old' products: Can we receive an update on the process for delisting an 'old' product/NDC?

Background: The delisting process currently states that delisting is accomplished by including a market end date in the SPL file. In many cases, labeling changes to legacy products (ie at the end of their lifecycle) have not been made for a long period of time. Therefore, product labeling may not have been converted to SPL, or has been only converted to SPL R3. Conversion to SPL R4 for these products, for the sole purpose of delisting, seems burdensome and wasteful. We would like to know if FDA is still considering an alternate, a less-burdensome delisting process for older products.

Suggestions raised in the past included: (1) The spreadsheet used for a short period in 2009 was one method, and we understand that this still required manual entry of the data by DRLS, which is not ideal for either sponsors or DRLS; (2) an abbreviated SPL file without content of labeling; (3) sponsors working directly with DRLS staff to identify 'old' products/NDCs for delisting.

Meeting Discussion Notes:

There are 2 processes involved in this question:

- Delisting: Removal of the product/NDC from the NDC directory.
- Removal of SPL from the Daily Med site (if R3 SPL has been submitted)

Delisting

DRLS agrees that sponsors should not have to create SPL R4 just to delist products that have been only listed via paper form. Sponsors may send an email or letter to DRLS to request a delisting. Please include the following identification information:

- Name of firm
- NDC #
- End marketing date (if no is date provided, the date of email will be used).

FDA will handle this manually and will send a confirmatory email of delisting. Manual delisting will result in the removal of the NDC code from the NDC directory immediately.

Since products may still be on pharmacy shelves and sold until the expiry date of the last lot, a sponsor should allow extra time to ensure that CMS reimbursements are processed.

This manual delisting by DRLS will not cause the product's SPL to be removed from Dailymed. **Post-meeting follow-up: If a product has SPL R3 posted on Daily Med, the process listed below should be used.**

Removal of SPL from the Dailymed Site

DRLS does not have any connection to the NLM/ Daily Med process.

NLM archives the SPL file when all products in the SPL file contain a market end date. A market end date is only available if the SPL is in R4 format. Thus, according to the current process, the sponsor must update their SPL to R4 in order to electronically remove their label from the current view in Daily Med.

Post-Meeting Note, based on communications with the SPL project manager and NLM:

If the product to be delisted has an SPL R3 posted on NLM, then the sponsor should delist by submitting an updated SPL R4 to the eList system. The process to be followed is:

- Convert the SPL R3 file to R4 format
- Enter a market end date for each product to be delisted
- Submit the SPL to eList, using the normal drug listing submission process

If only one (of multiple) package size is being delisted:

- submit the R4 SPL with the package size included
- modify the SPL file to delete the package size (that is being delisted)
- resubmit the modified R4 SPL (without the package size)

If all products in the SPL file have a market end date, NLM will remove the SPL from the current view and archive it.

Meeting Attendees:

Paul Loebach - FDA

Dave Mazyck - FDA

Leyla Rahjou-Esfandiary - FDA

Pat Cowall-Hanover - Lilly

Michelle Halliez - BMS

Jessica Dunn-Skorupski - J and J

Dragan Obradovich - Abbott

Kim Shaw - Abbott

Nadine Lewis - AstraZeneca

Ann Howett - BMS

Jacquelyn Mohns - BMS

Marilyn Maxwell - Boehringer-Ingelheim

Marcia Howard - Consumer Healthcare Products Association

Howard Shatz - DCLab

Theresa Brunone - GSK

Paula Markert - GSK

Jean Kirkeleit-Davis - Hospira

Jim Gallagher - IPS

Beth Macioci - J and J

Kathleen Parker- Merck

Kathy Olgers - Perrigo

Adam Weinberg - Pfizer

Warren Sunshine - Pfizer

Ava Johnson - Pfizer

Jacqueline Nelson - Purdue

Gary Saner - Reed Technologies
Tara Petrowicz - Teva
Ruth Kirkner - Teva